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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,535	04/05/2007	Ian Carroll	STAN-332	8908

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,535	CARROLL ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 14 March 2008 have been entered. Claims 11 and 13 – 16 are canceled; claims 1 – 10 and 12 are pending and under examination.

Withdrawn Rejections

2. The following rejections and objections set forth in the previous office action are withdrawn:

A. Any rejection of a claim now canceled is moot.

B. The rejection under 35 USC 112, first paragraph, is withdrawn in light of the arguments and amendments. The examiner concedes that since it was well known in the prior art that coronary artery disease (see Chester (2000) Pain 87:103-105), vasospasms generally and Raynaud's disease in particular (see Di Lorenzo (1998) JSLS: Journal of the Society of Laparoendoscopic Surgeons 2(3):249-253), cerebral vasospasms (Treggiari (2003) Stroke 34:961-967), and vasospastic disease which is a peripheral vascular disease (Di Lorenzo) can all be treated by blocking the activity of sympathetic ganglia, it is reasonable that all of these diseases could be treated by administration of botulinum toxin as claimed, since this toxin blocks the activity of the sympathetic ganglia. Thus the skilled artisan could make and use the full scope of the invention as claimed.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 3 and 5 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) Autonomic Neuroscience 102:8-12 in view of Donovan (U.S. Patent Application Publication 2001/0023243, cited in previous office action).

As set forth in the previous office action, Kim teaches sympathetically mediated chronic pain is mediated by the sympathetic ganglion (see p. 8 first paragraph). The reference teaches administration of botulinum toxin type A, recited in claims 1 and 2. The reference teaches that the dose used was 2 - 10 units per kilogram of body weight, administered to rabbits which is within the range recited in claim 3, given that rabbits weigh less than 30 kg. The reference teaches administration to the superior cervical ganglion as recited in claim 5 - 6. However Kim does not teach administration to humans, and does not explicitly teach percutaneous injection as recited in claim 1. Rather Kim teaches administration rabbits and teaches direct administration to the ganglion following surgical opening of the skin and underlying tissues.

Donovan teaches that botulinum toxin A, recited in claims 1 – 2, can be administered to cervical ganglia in humans via percutaneous injection, which is on point to the newly-added limitation in claim 1. However Donovan does not teach administration of this toxin for treatment of chronic pain, as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of Kim et al. to treat humans in pain and to do so via percutaneous injection, with a reasonable expectation of success. The motivation to do so would be to effectively treat pain in humans. It is reasonable to expect success as the rabbits used by Kim are a model of human physiology, the reference by Kim teaches the appropriate dose, and Kim suggests that the side effects are minimal and that the toxin should be used for treatment of sympathetic pain. Additionally, Kim contemplates modifications of the method for clinical use, which implies treatment of humans, and specifically notes that the exact dose may have to be varied (see Kim, p. 11, last two paragraphs). Donovan provides a reasonable expectation of success in administration of the toxin to humans via the percutaneous route, and selection of this mode of administration would be advantageous as it would obviate the need for the surgical procedures used by Kim, thereby leading to decreased risk of infection and discomfort in the patient.

In the previous office action, a similar rejection was made over Kim alone. Applicant

argued in the remarks filed 14 March 2008 that the reference by Kim is on point to miosis, and not to relief of pain, by botulinum toxin A. Applicant argues that there is not a significant correlation between miosis as measured by Kim and relief of pain, as claimed. Additionally, according to applicant, Kim teaches the use of botulinum toxin as a neurolytic, and the present specification teaches against using neurolytics because of their deleterious effects.

Applicant's arguments have been fully considered but they are not persuasive. The examiner acknowledges that Kim did not explicitly measure pain or nociception in the animals. However, Kim relied upon the well-known fact that certain forms of chronic pain are meditated by the sympathetic ganglia. In the very first sentence of the introduction, Kim states that "[s]ympathetic block is one of the most important methods of treating chronic pain." The introduction goes on to state which methods are known to treat pain (neurolysis of, or destruction of neurons within, sympathetic ganglia) and discloses compounds known to be effective in such methods, including alcohol and phenol. Kim discloses certain problems faced by patients who have received such treatment, including paraplegia and lower extremity paralysis (p. 8 second column). The miosis (pupil constriction) measured by Kim is a way to determine the functioning of the superior cervical ganglion; see for example Purves et al. Neuroscience 2001. 2nd Edition, Chapter 21 (Visceral Motor System), Box B, enclosed with this office action. Purves teaches that miosis is a decreased diameter of the pupil (first paragraph) and is the result of damage to and decreased activity of the superior cervical ganglion (second paragraph; see also Figure B and corresponding legend). Kim measured miosis following injection of botulinum toxin into the ganglion in order to determine the degree to which the toxin blocks sympathetic ganglion activity. Kim concluded that "BTA acted on the sympathetic neurons of the SCG" (p. 11 second paragraph) and indicates that "BTA has usefulness as a neurolytic agent for sympathetically mediated pain" (p. 11 final sentence). Because Kim teaches that chronic pain is mediated by the sympathetic ganglia and that botulinum toxin A decreases the activity of the neurons in those ganglia, the authors conclude that it should be useful in blocking chronic pain. Clearly there is a nexus between miosis and chronic pain, as both are mediated by the same ganglia.

To the extent that applicant is arguing about the specification cautioning against use of "neurolytic" agents, Kim teaches the advantages of botulinum toxin over other neurolytics; see p. 11, first column, final paragraph. Botulinum toxin is not a true neurolytic, as it does not kill the cells. Rather, it prevents release of acetylcholine. It appears that Kim is using the term

"neurolytic" in a manner different from applicant – i.e. Kim is using the term to include agents which decrease neural activity, and does not limit the term to those agents which kill neurons. Since the reference by Kim clearly points to the efficacy of botulinum toxin A in treatment of chronic pain, the reference suggests the same thing which applicant has done, independent of whether the toxin is termed a neurolytic or not.

Finally, applicant argues that the rabbit model used by Kim may not be predictive of success in humans. While certain models of pain may not be fully predictive of success in humans, there is no particular reason to doubt that the findings of Kim could be extended to humans. The finding that botulinum toxin inhibits activity of the superior cervical ganglion in rabbits could reasonably be extended to humans, based on the similar anatomy. Additionally, absolute success is not required in determinations of obviousness, rather the standard is a reasonable expectation of success; see MPEP § 2143.02(I). Applicant cites the abstract of the reference by Onal et al. (note no copy of the article was provided) as supporting the argument that when cholinergic drugs are used, there is not a strong correlation between pain and miosis. The examiner has obtained a copy of the reference (see attached) and it is clear that Onal used intravenous injections. This route is not the same as claimed (percutaneous injection) and would be expected to have quite different effects. The method of Onal would allow for the drug to be distributed over the entire body; little if any would be expected to enter the ganglia. The methods of Kim and Donovan, each of which is on point to direct administration of the toxin to the sympathetic ganglia, would result in the drug being concentrated in those ganglia. Thus it is improper to extend the findings of Onal, which teach a lack of correlation between miosis and pain for cholinergic drugs, to the instant situation, as Kim teaches that botulinum toxin A, when administered directly into the ganglia, results in inactivation of them.

Given that Donovan teaches that blocking sympathetic ganglia with other agents is known to treat pain (see paragraph [0090]) and that Donovan also teaches that certain other conditions (e.g. thyroid disease) can be treated by percutaneous administration of botulinum toxin to the ganglia, the artisan of ordinary skill would have had a reasonable expectation of success in administering this toxin to the appropriate ganglia for treatment of pain.

4. Claims 1 – 3 and 5 – 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243 as applied to claims 1 – 3 and 5 – 6 above, and further in view of Erickson (1993. Radiology 188:707-709).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above. However, neither of these references teaches administering a local anesthetic as a sympathetic block and identifying chronic pain as being mediated by the sympathetic nervous system as recited in claim 7.

The teachings of Erickson have been set forth in the previous office action. Briefly, Erickson teaches methods of administering local anesthetic, including lidocaine, bupivarcaine, and buprenophrine as sympathetic blocks. Erickson teaches the method is successful in human patients, as recited in claim 1, and leads to pain relief, including complete pain relief which is more than 50% of the perceived pain as recited in claim 7 (see results section). However Erickson does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to include the step of administering a short-acting local anesthetic as a sympathetic block, as taught by Erickson, when performing the methods of claims 1 – 3, as suggested by Kim and Donovan, thereby arriving at the invention of claim 7. The motivation to do so would be to ensure that the pain experienced by the patient is in fact mediated by the sympathetic ganglia. Performing this step would be advantageous, as it would ensure that those patients whose pain is not mediated by sympathetic ganglia will not be exposed to the toxin. Thus by performing the step taught by Erickson and recited in claim 7, the artisan would ensure identification of the patients most amenable to treatment.

Applicant argues, on pp, 8 – 9 of the remarks that Erickson fails to cure the deficiencies of Kim. The reasons why Kim and Donovan render obvious the methods of claims 1 – 3 obvious are set forth in detail above. The reference by Erickson teaches the additional steps recited in claim 7. The examiner has provided a sound reason why an artisan of ordinary skill would have found it obvious to perform these steps. Applicant argues, on p. 9 of the remarks, that different mechanisms are involved in the methods taught by Erickson and the claimed invention. This argument is not persuasive. First, it is noted that applicant is not claiming a mechanism, but a method of treating pain. Thus the question is not whether the mechanisms are identical, but rather an artisan of ordinary skill would have found the claimed methods obvious. Second, the use of a fast-acting drug such as lidocaine taught by Erickson would have

been particularly advantageous, as it would allow for rapid determination of which patients are actually suffering from sympathetically mediated pain. While the mechanism of action is not identical to that of botulinum toxin, the nerves in the ganglia would still be inactivated by the methods taught in Erickson, thus the steps would be suitable for identification of patients as explained earlier.

5. Claims 1 – 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243 as applied to claims 1 – 3 and 5 – 6 above, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275, published 27 December 2001).

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above. However, neither of these references teaches administration to a sympathetic ganglion and achieving a block of the splanchnic nerve when pain is in the lower extremities, as recited in claim 4.

Brushey teaches that the sphlanic nerve should be blocked when pain is in the lower extremities, by blocking the celiac plexus (paragraphs [0004] – [0005]). However Brushey does not teach administration of botulinum toxin as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to modify the methods rendered obvious by Kim and Donovan such that when the pain is present in the lower extremities, the toxin would be given to block the splanchnic nerve. The motivation to do so would be to effectively block pain, as Brushey teaches this is the nerve to be blocked when pain is present in the lower extremity.

Applicant indicated (remarks, p. 9) that the reference by Brushey “teaches certain locations for peripheral pain management” but argued that neither this reference nor the reference by Kim teaches or renders obvious selection of botulinum toxin for administration. For the reasons set forth above, the examiner has concluded that it would have been obvious to one of ordinary skill in the art to administer botulinum toxin by percutaneous injection as claimed. The reference by Brushey teaches the specific regions where the inactivating agent (here, the toxin) should be administered, as recited in claim 4.

6. Claims 1 – 3, 5 – 6, and 8 – 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henard (1982. Arch Mal Coeur 75(11):1317-1320, cited on IDS filed 22 February 2007) in view of Kim (2002) and Donovan 2001/0023243.

Henrard teaches treatment of coronary vasospasm which is on point to coronary artery disease recited in claim 8 and is a peripheral vascular disease as recited in claims 8 – 9. Henrard teaches that the spasms can be treated by homolateral thoracic sympathectomy, i.e. surgical removal of a sympathetic ganglion (see abstract translation on p. 1320). Such surgical removal will necessarily stop activity of the sympathetic ganglion, which is on point to claims 8 and 9. However Henrard does not teach administration of boutlinum toxin and does not teach percutaneous injection as recited in claims 8 and 9.

The reasons why claims 1 – 3 and 5 – 6 are obvious over Kim in view of Donovan are set forth above. Kim teaches pain relief by administering botulinum toxin to a sympathetic ganglion, which is on point to claims 8 and 10, and the doses as recited in claim 12. However, Kim does not teach administering botulinum toxin to patients with cardiovascular conditions as recited in claim 8, or the specific diseases recited in claim 9. Donovan teaches administration of botulinum toxin to sympathetic ganglia by percutaneous injection, but does not explicitly teach using this method to treat peripheral vascular disease in general, as recited in claim 9 or coronary artery disease in particular, as recited in claim 8.

It would have been obvious to one of ordinary skill in the art to modify the method of Henrard by administering botulinum toxin to the sympathetic ganglion instead of removing the sympathetic ganglion, thereby arriving at the invention of claims 8 – 10 and 12. Henrard teaches that inactivating the ganglion by removal is sufficient for treatment of spasm, and using botulinum toxin for inactivation, as taught by Kim, would be advantageous as it would be less invasive. Additionally, selection of the method of administration taught by Donovan, namely percutaneous injection, would be advantageous as it would allow for the toxin to penetrate and inactivate the ganglia without requiring surgery. Note claim 10 is included in this rejection as it does not recite any additional starting materials or steps, but rather recites effects which will happen upon administration.

On pp. 9 – 10 of the remarks, applicant argues that "Henard et al. fail to teach the novel use of botulinum toxin to decrease sympathetic activation for the treatment of cardiovascular conditions". The examiner agrees with this statement; if every limitation of the relevant claims were taught by Henard, the rejection would have been set forth under 35 USC 102 rather than

35 USC 103. However, the deficiency of Henard (administration of botulinum toxin to inactivate sympathetic ganglia rather than surgical removal to inactivate for treatment of the coronary vasospasm) is cured by Kim. As discussed at length above, Kim teaches that botulinum toxin, when injected into a sympathetic ganglion, is sufficient to inactivate it. Additionally, Donovan provides guidance to select the percutaneous injection route now claimed, as he teaches that this is an effective way to administer this toxin to the ganglia, and selection of this route would be advantageous in that it would obviate the need for invasive surgery and the accompanying risks of infection.

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
June 19, 2008